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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/619,754	07/14/2003	Birgit Bossenmaier	GNE-0114	3323

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EXAMINER	
HOLLERAN, ANNE L	
ART UNIT	PAPER NUMBER
1643	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/619,754	BOSSENMAIER ET AL.	
	Examiner	Art Unit	
	ANNE L. HOLLERAN	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 June 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *23-28,40-52 and 64-73* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *23-28,40-52 and 64-73* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *8/07*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The Office communication mailed 8/29/2007 is VACATED.

The amendment filed 6/8/2007 is acknowledged. Claims 23-28, 40-52 and 64-73 are pending and examined on the merits.

Claim Rejections Withdrawn:

Claim Rejections - 35 USC § 112

The rejection of claims 23-28, 40-52, and 64-73 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is withdrawn in view of the amendment to claims 23, 47 and 71 removing the phrase "a significant level of phosphorylation".

The rejection of claims 23-28, 40-52 and 64-73 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement is withdrawn in view of the amendment removing the phrase "a significant level of phosphorylation".

Claim Rejections - 35 USC § 102

The rejection of claims 23-28, 40, 42, 46-52, 64, 66, and 70 under 35 U.S.C. 102(b) as being anticipated by Thor (Thor, A.D. et al., Journal of Clinical Oncology, 18(18): 2000, 3230-3239, 2000) is withdrawn in view of the amendment adding a step of either subjecting the tumor cells to treatment with an antibody inhibiting the association of HER2 with another member of

the ErbB receptor family, or of administering to a subject an antibody that inhibits the association of HER2 with another member of the ErbB receptor family.

The rejection of claims 23-28, 40, 42-44, 47-52, 64, and 66-68 under 35 U.S.C. 102(b) as being anticipated by Wildenhain (Wildenhain, Y. et al., Oncogene, 5(6): 879-883, 1990; abstract only) is withdrawn in view of the amendment adding a step of either subjecting the tumor cells to treatment with an antibody inhibiting the association of HER2 with another member of the ErbB receptor family, or of administering to a subject an antibody that inhibits the association of HER2 with another member of the ErbB receptor family.

The rejection of claims 23-28, and 42-44 under 35 U.S.C. 102(b) as being anticipated by Xu (Xu, F.J. et al. Int. J. Cancer, 59: 242-247, 1994) is withdrawn in view of the amendment adding a step of subjecting the tumor cells to treatment with an antibody inhibiting the association of HER2 with another member of the ErbB receptor family.

The rejection of claims 23-28, and 42-44 under 35 U.S.C. 102(b) as being anticipated by Ignatoski (Ignatoski, K.M.W., et al., Endocrinology, 140: 3615-3622, 1999) is withdrawn in view of the amendment adding a step of subjecting the tumor cells to treatment with an antibody inhibiting the association of HER2 with another member of the ErbB receptor family.

The rejection of claims 23-28, 40, 42-44, 47-52, 64, 66, and 70 under 35 U.S.C. 102(b) as being anticipated by DiGiovanna (DiGiovanna, M.P. et al. Cancer Research 55: 1946-1955,

1995; of record) is withdrawn in view of the amendment adding a step of subjecting the tumor cells to treatment with an antibody inhibiting the association of HER2 with another member of the ErbB receptor family.

Claim Rejections - 35 USC § 103

The rejection of claims 23, 41, 47, 65 and 71-73 under 35 U.S.C. 103(a) as being unpatentable over DiGiovanna (DiGiovanna, M.P. et al. Cancer Research 55: 1946-1955, 1995) in view of Terstappen (US 6,365,362; issued Apr. 2, 2002; effective filing date Nov. 30, 1998) is withdrawn in view of the amendment adding a step of either subjecting the tumor cells to treatment with an antibody inhibiting the association of HER2 with another member of the ErbB receptor family, or of administering to a subject an antibody that inhibits the association of HER2 with another member of the ErbB receptor family.

The rejection of claims 23, 43, 45, 47, 67 and 69 under 35 U.S.C. 103(a) as being unpatentable over DiGiovanna (DiGiovanna, M.P. et al. Cancer Research 55: 1946-1955, 1995) is withdrawn in view of the amendment adding a step of either subjecting the tumor cells to treatment with an antibody inhibiting the association of HER2 with another member of the ErbB receptor family, or of administering to a subject an antibody that inhibits the association of HER2 with another member of the ErbB receptor family

New Grounds of Rejection:

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 23-28, 40-52, 64-73 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 23, 47 and 71 are indefinite because the stated purpose of each of the methods does not correlate with the steps set forth. In the case of claim 23, the stated purpose is the identification of HER2-positve tumor cells, whereas the steps comprise an identification step and then a subjecting step. It is not clear how the subjecting step accomplishes the stated purpose of identifying HER-2 positive tumor cells as responsive to treatment with an antibody that inhibits the association of HER2 with another member of the ErbB receptor family. In the case of claim 47, the stated purpose is the prediction of the response of a subject diagnosed with a HER2-positive tumor to treatment with an antibody inhibiting the association of HER2 with another member of the ErbB receptor family, whereas the steps comprise an identification step and then an administration step. It is not clear how the administration step accomplishes the stated purpose of predicting response of a subject to treatment with an antibody that inhibits the association of HER2 with another member of the ErbB receptor family. In the case of claim 71, the stated purpose is the identification of a subject as responsive to treatment with an antibody inhibiting the association of HER2 with another member of the ErbB receptor family, whereas the steps comprise a determination step (determining presence of phosphorylation in circulating

tumor cells) and then an administration step. It is not clear how the administration step accomplishes the stated purpose of identifying a subject as responsive to treatment with an antibody that inhibits the association of HER2 with another member of the ErbB receptor family.

Claim 42 is indefinite because "the tumor" lacks antecedent basis in claim 23, from which claim 42 depends.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out

the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 47-52, 64, and 66-70 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sliwkowski (US 6,949,245; issued Sep. 27, 2005; effective filing date is June. 25, 1999) in view of Bangalore (Bangalore, L., et al. Proc. Natl. Acad. Sci, USA, 89: 11637-11641, 1992) or DiGiovanna (supra).

The applied reference has a common inventor with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art only under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 103(a) might be overcome by: (1) a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not an invention "by another"; (2) a showing of a date of invention for the claimed subject matter of the application which corresponds to subject matter disclosed but not claimed in the reference, prior to the effective U.S. filing date of the reference under 37 CFR 1.131; or (3) an oath or declaration under 37 CFR 1.130 stating that the application and reference are currently owned by the same party and that the inventor named in the application is the prior inventor under 35 U.S.C. 104, together with a terminal disclaimer in accordance with 37 CFR 1.321(c). This rejection might also be overcome by showing that the reference is disqualified under 35 U.S.C. 103(c) as prior art in a rejection under 35 U.S.C. 103(a). See MPEP § 706.02(l)(1) and § 706.02(l)(2).

Claims 47-52, 64, and 66-70 are drawn to methods comprising the administration of an antibody that inhibits the association of HER2 with another member of the ErbB receptor family wherein the subject is one for which a biological sample has been tested for the presence of a phosphorylated ErbB receptor.

Sliwkowski teaches a method of treating a subject with an anti-HER2 antibody, rhuMab 2C4, where the subject has a cancer that may be characterized as having excessive activation of an ErbB receptor (see column 46 lines 28-35). Sliwkowski fails to teach a method of screening subjects for those that have an excessive activation of an ErbB receptor.

Bangalore teaches a method of measuring phosphorylated ErbB2 (HER2) using an antibody specific for phosphorylated ErbB2 or phosphorylated EGFR. Bangalore teaches that such a measurement would be useful to measure ErbB2 activation levels directly on biopsy specimens (see abstract; see page 11637, right column). Bangalore teaches that ErbB2 amount may not be a good prognostic indicator, but instead receptor activity may be a better prognostic indicator (see 11637, left column).

DiGiovanna teaches use of immunohistochemistry on formalin-fixed and paraffin-embedded surgical specimens form human breast tumors using the NP2A antibody, which is specific for phosphorylated HER2 (p185). DiGiovanna also teaches that the extent of HER2 tyrosine phosphorylation varies considerable and that it is highly likely that measurement of HER2 signaling activity as opposed to HER2 abundance will greatly enhance methods that use detection of HER2 for prognosis and treatment decisions, and that tumors most vulnerable to anti-HER2 antibodies will be those that are dependent on HER2 signaling for growth (ses page 1954, 1st column).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have combined the teachings of Sliwkowski with those of Bangalore or DiGiovanna to make the claimed methods, because Sliwkowski teaches a method for the treatment of cancers where an ErbB receptor is activated and Bangalore or DiGiovanna teaches that phosphorylation of Her2 is a measurement of Her2 signalling activity. Therefore, one of skill in the art would have been motivated to used the method of Bangalore or DiGiovanna to screen for subjects most likely to respond to the 2C4 antibody.

Claims 47-52, 65-73 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sliwkowski (US 6,949,245; issued Sep. 27, 2005; effective filing date is June. 25, 1999) in view of Bangalore (Bangalore, L., et al. Proc. Natl. Acad. Sci, USA, 89: 11637-11641, 1992) or DiGiovanna (supra).

The applied reference has a common inventor with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art only under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 103(a) might be overcome by: (1) a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not an invention "by another"; (2) a showing of a date of invention for the claimed subject matter of the application which corresponds to subject matter disclosed but not claimed in the reference, prior to the effective U.S. filing date of the reference under 37 CFR 1.131; or (3) an oath or declaration under 37 CFR 1.130 stating that the application and reference are currently owned by the same party and that the inventor named in the application is the prior inventor under 35 U.S.C. 104, together with a terminal disclaimer in

accordance with 37 CFR 1.321(c). This rejection might also be overcome by showing that the reference is disqualified under 35 U.S.C. 103(c) as prior art in a rejection under 35 U.S.C. 103(a). See MPEP § 706.02(l)(1) and § 706.02(l)(2).

Claims 47-52, 65-73 are drawn to methods comprising the administration of an antibody that inhibits the association of HER2 with another member of the ErbB receptor family wherein the subject is one for which a biological sample that is a sample of circulating tumor cells has been tested for the presence of a phosphorylated ErbB receptor.

Sliwkowski teaches a method of treating a subject with an anti-HER2 antibody, rhuMab 2C4, where the subject has a cancer that may be characterized as having excessive activation of an ErbB receptor (see column 46 lines 28-35). Sliwkowski fails to teach a method of screening subjects for those that have an excessive activation of an ErbB receptor.

Bangalore teaches a method of measuring phosphorylated ErbB2 (HER2) using an antibody specific for phosphorylated ErbB2 or phosphorylated EGFR. Bangalore teaches that such a measurement would be useful to measure ErbB2 activation levels directly on biopsy specimens (see abstract; see page 11637, right column). Bangalore teaches that ErbB2 amount may not be a good prognostic indicator, but instead receptor activity may be a better prognostic indicator (see 11637, left column).

DiGiovanna teaches use of immunohistochemistry on formalin-fixed and paraffin-embedded surgical specimens form human breast tumors using the NP2A antibody, which is specific for phosphorylated HER2 (p185). DiGiovanna also teaches that the extent of HER2 tyrosine phosphorylation varies considerable and that it is highly likely that measurement of

HER2 signaling activity as opposed to HER2 abundance will greatly enhance methods that use detection of HER2 for prognosis and treatment decisions, and that tumors most vulnerable to anti-HER2 antibodies will be those that are dependent on HER2 signaling for growth (ses page 1954, 1st column).

Neither Bangalore nor DiGiovanna teaches assessing ErbB phosphorylation status on a sample of circulating tumor cells.

However, Terstappen teaches that carcinoma cells in the blood may be assay immunocytochemically to characterize the circulating tumor cells. Terstappen teaches that the methods may be used to monitor patients for recurrence of cancer or for response to therapy, and teaches that levels of tumor markers such as Her2 may be assessed (see abstract; and column 8, lines 29-57 and column 9, line 54 – column 10, line 51).

Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have modified Bangalore or DiGiovanna's method so that it could be used in the measurement of Her2 phosphorylation status of circulating tumor cells. One would have been motivated to have combined the teachings of Bangalore or DiGiovanna with that of Terstappen because collecting a blood sample to analyze the Her-2 status of circulating cancer cells is less invasive than collecting a tissue sample from the cancer. Furthermore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have combined the teachings of Sliwkowski with those of Banglaore, DiGiovanna and Terstappen to make the claimed methods, because Sliwkowski teaches a method for the treatment of cancers where an ErbB receptor is activated and Bangalore or DiGiovanna teaches that phosphorylation of Her2 is a measurement of Her2 signalling activity. Therefore, one of

skill in the art would have been motivated to used the method of Bangalore or DiGiovanna to screen for subjects most likely to respond to the 2C4 antibody.

Claims 23-28, 40 and 42-45 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bangalore (supar) in view of DiGiovanna (supra), and further in view of Lewis (Lewis, G. D., et al., Cancer Research, 56: 1457-1465, 1996).

The claims are drawn to methods of detecting in a sample of tumor cells the presence of a phosphorylated ErbB receptor, where the ErbB receptor may be an ErbB2 receptor, and then treating the tumor cells with an antibody that inhibits the association of HER2 with another member of the ErbB receptor family.

Bangalore teaches a method of measuring phosphorylated ErbB2 (HER2) using an antibody specific for phosphorylated ErbB2 or phosphorylated EGFR. Bangalore teaches that such a measurement would be useful to measure ErbB2 activation levels directly on biopsy specimens (see abstract; see page 11637, right column). Bangalore teaches that ErbB2 amount may not be a good prognostic indicator, but instead receptor activity may be a better prognostic indicator (see 11637, left column).

DiGiovanna teaches use of immunohistochemistry on formalin-fixed and paraffin-embedded surgical specimens form human breast tumors using the NP2A antibody, which is specific for phosphorylated HER2 (p185). DiGiovanna also teaches that the extent of HER2 tyrosine phosphorylation varies considerable and that it is highly likely that measurement of HER2 signaling activity as opposed to HER2 abundance will greatly enhance methods that use detection of HER2 for prognosis and treatment decisions, and that tumors most vulnerable to

anti-HER2 antibodies will be those that are dependent on HER2 signaling for growth (ses page 1954, 1st column).

Neither Bangalore nor DiGiovanna teach a method comprising a further step of treating samples with an antibody that inhibits the association of HER2 with another member of the ErbB receptor family.

However, Lewis teaches that monoclonal antibody 2C4, which has the same activity and binding specificity as that of rhuMAb 2C4 (the humanized version of 2C4) inhibits tyrosine phosphorylation due to heregulin addition to human breast and ovarian tumor cells. Thus, Lewis teaches that 2C4 is an antibody that blocks activation of HER2.

Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have tested the activity of rhuMAb 2C4 on samples of tumor cells that exhibited activated ErbB2 because Lewis teaches that the mechanism by which 2C4 inhibits ErbB2 activity is to inhibit the activation of ErbB2 by heregulin. One would have been motivated to combine the teachings of the Bangalore, DiGiovanna and Lewis to make a method that tests the efficacy of rhuMAb 2C4 on a patient's tumor sample to decrease phosphorylation of an ErbB receptor.

Conclusion

No claim is allowed.

Please note: NO deposit rejection is required for claims reciting rhuMab 2C4, because the complete structure of this antibody is provided on page 26 of the specification.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anne Holleran, whose telephone number is (571) 272-0833. The examiner can normally be reached on Monday through Friday from 9:30 am to 5:00 pm. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms, can be reached on (571) 272-0832. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (571) 272-1600.

Papers related to this application may be submitted to Group 1600 by facsimile transmission. The faxing of such papers must conform to the notice published in the Official

Gazette, 1096 OG 30 (November 15, 1989). The Official Fax number for Group 1600 is (571) 273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll free).

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Patent Examiner
May 11, 2009
/Alana M. Harris, Ph.D./
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